GSK's Human Rotavirus Vaccine ROTARIX®

Presentation to the ACIP

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Human RV Vaccine - *Rotarix*

- Oral vaccine, 2-dose series
- Lyophilized vaccine + liquid diluent ($CaCO_3$)
  - 1 mL per dose
  - Each dose: ≥10^6 $CCID_{50}$ of live, attenuated HRV strain
- Licensed in 100+ countries; initial license 2004
- BLA submitted to FDA: 1 June 2007
- ACIP presentation: 25 October 2007
- **FDA approval: 3 April 2008**

Overview: Efficacy Data

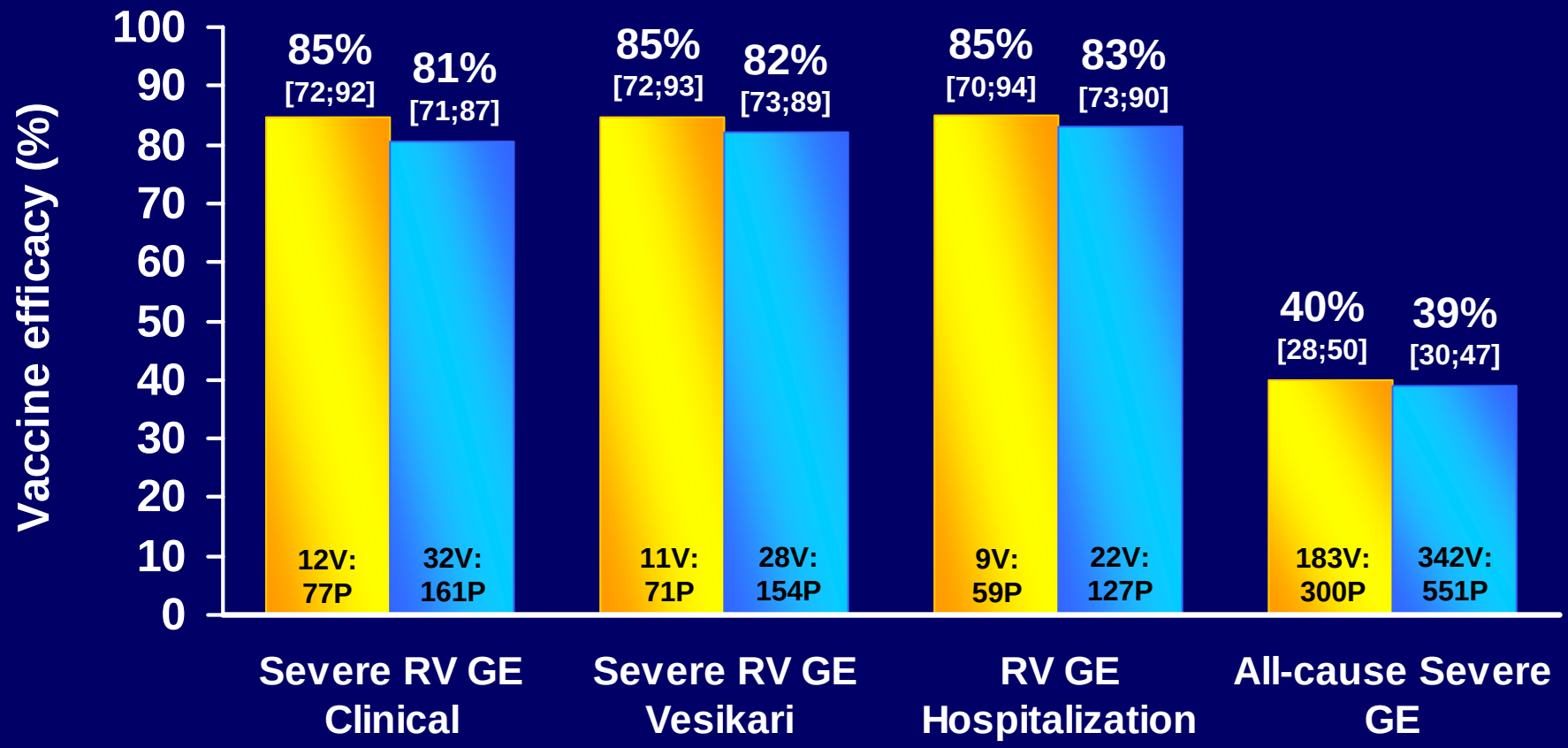
Phase III

- Study 023: Latin America
- Study 036: Europe

Efficacy Latin America (Study 023)

From 2 weeks post-dose 2 until 12 months of age (ATP cohort)

From 2 weeks post-dose 2 until 24 months of age (ATP cohort)

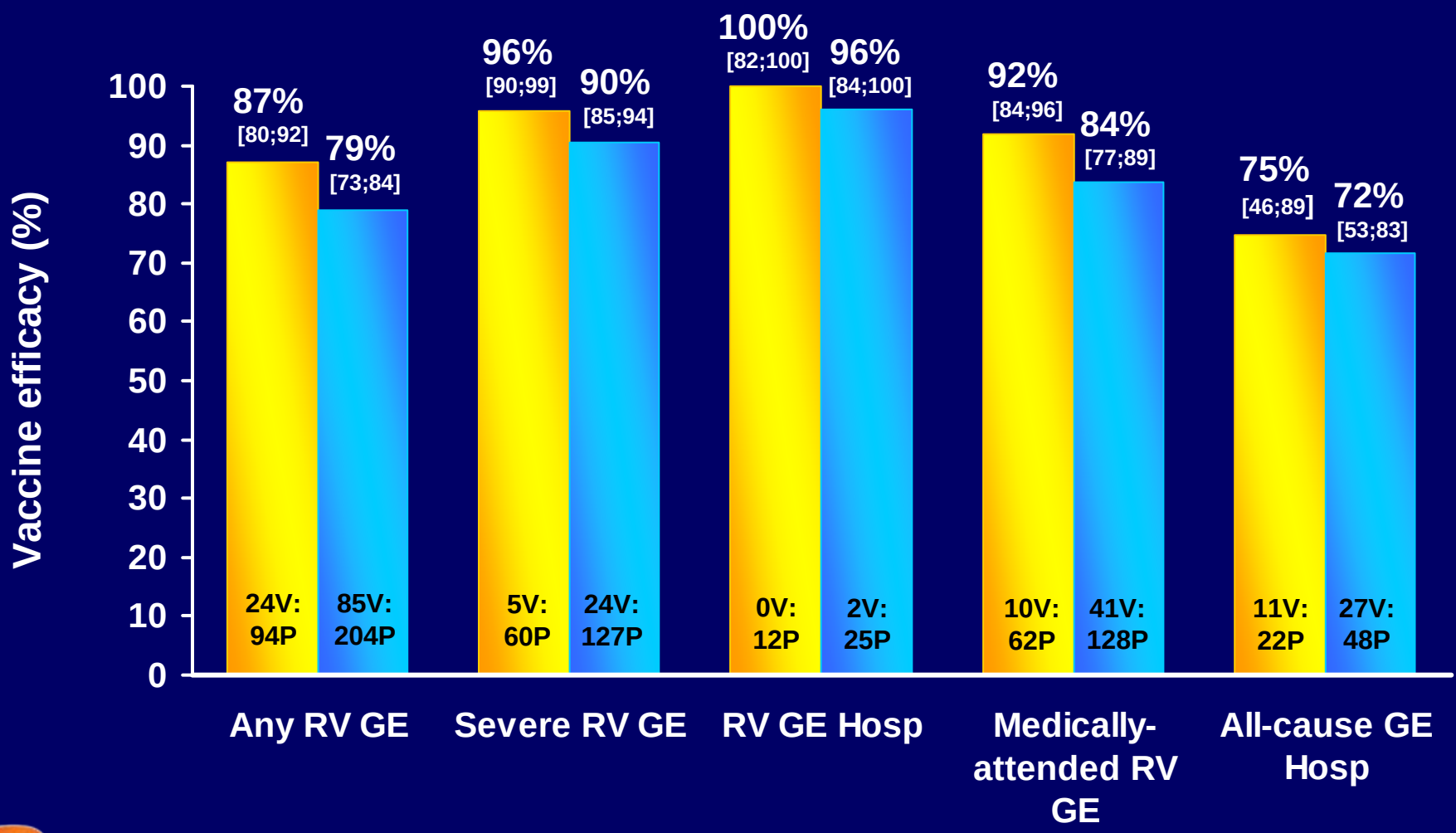


randomization 1:1

Efficacy Europe (Study 036)

From 2 weeks post-dose 2 until end of the 1st RV season (ATP cohort)

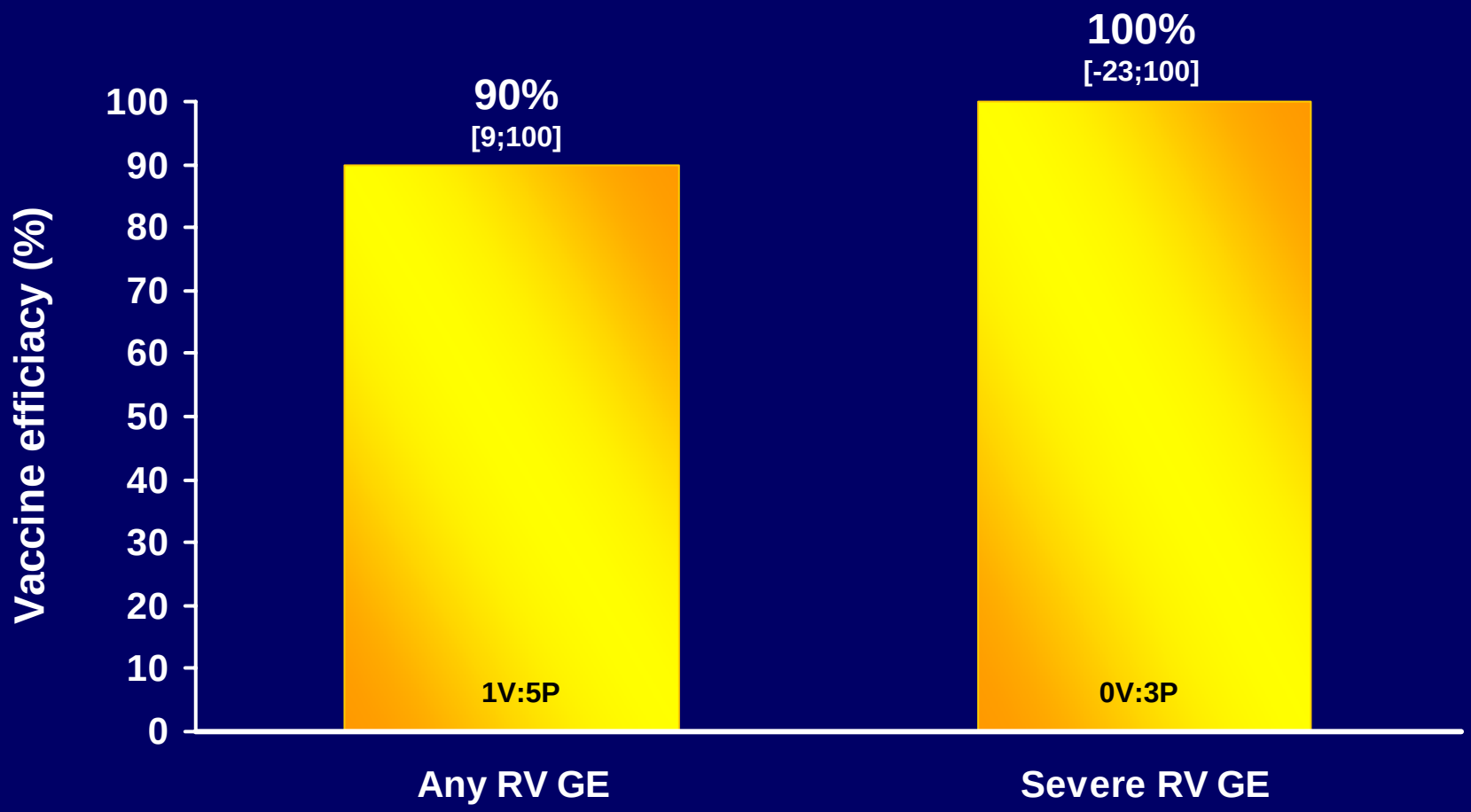
From 2 weeks post-dose 2 until end of the 2nd RV season (ATP cohort)



randomization 2:1

Efficacy Europe (Study 036)

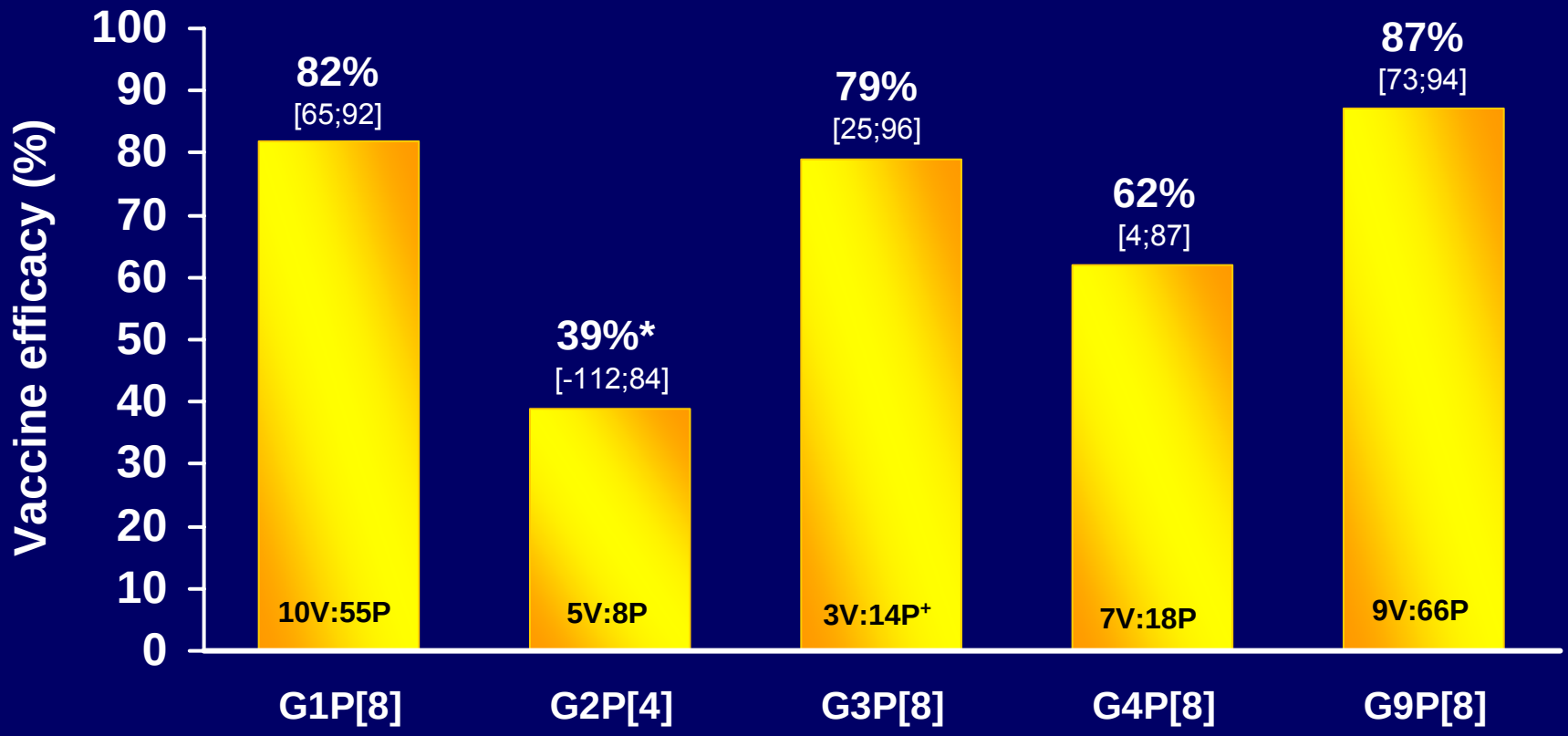
From Dose 1 up to before Dose 2 (Total Vaccinated Cohort)



TVC = all subjects who received at least one dose regardless of protocol adherence

Type-specific Efficacy Latin America (Study 023) - severe RV GE

From 2 weeks post-dose 2 until 24 months of age (ATP cohort)



+ one episode was P[6]

**Not statistically significant*

randomization 1:1

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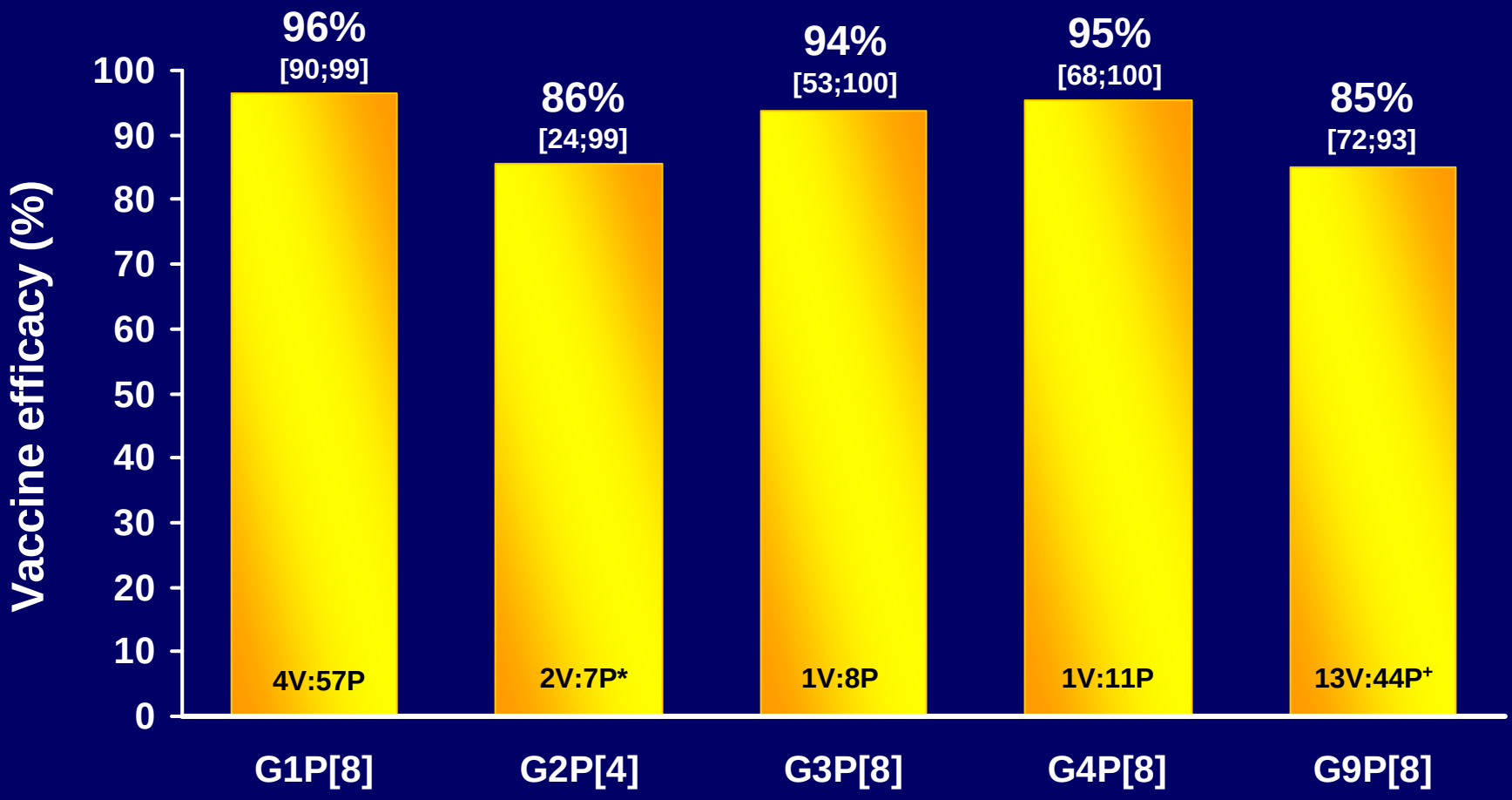
Type-specific Efficacy Europe (Study 036) - Severe RV GE

From 2 weeks post-dose 2 until end of the 2nd RV season (ATP cohort)



* P genotype not typable for one episode, + P[8] genotype not detected for one episode

randomization 2:1

Immunogenicity – Coadministered Vaccines US Study 060

- Randomized 1:1, controlled, open label
- 1º Objective: Non-inferiority immunogenicity ***Rotarix*** + coads vs. coads alone
- N=484 (1:1)

	Month of Age					
	2	**3**	**4**	**5**	**6**	**7**
Co-Ad group	***Rotarix*** ***Pediarix*** ***Prevnar*** ***ActHIB***		***Rotarix*** ***Pediarix*** ***Prevnar*** ***ActHIB***		***Pediarix*** ***Prevnar*** ***ActHIB***	**Blood Sample Serology Testing**
Sep-Ad group	***Pediarix*** ***Prevnar*** ***ActHIB***	***Rotarix***	***Pediarix*** ***Prevnar*** ***ActHIB***	***Rotarix***	***Pediarix*** ***Prevnar*** ***ActHIB***	**Blood Sample Serology Testing**

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Immunogenicity – Coadministered Vaccines US Study 060

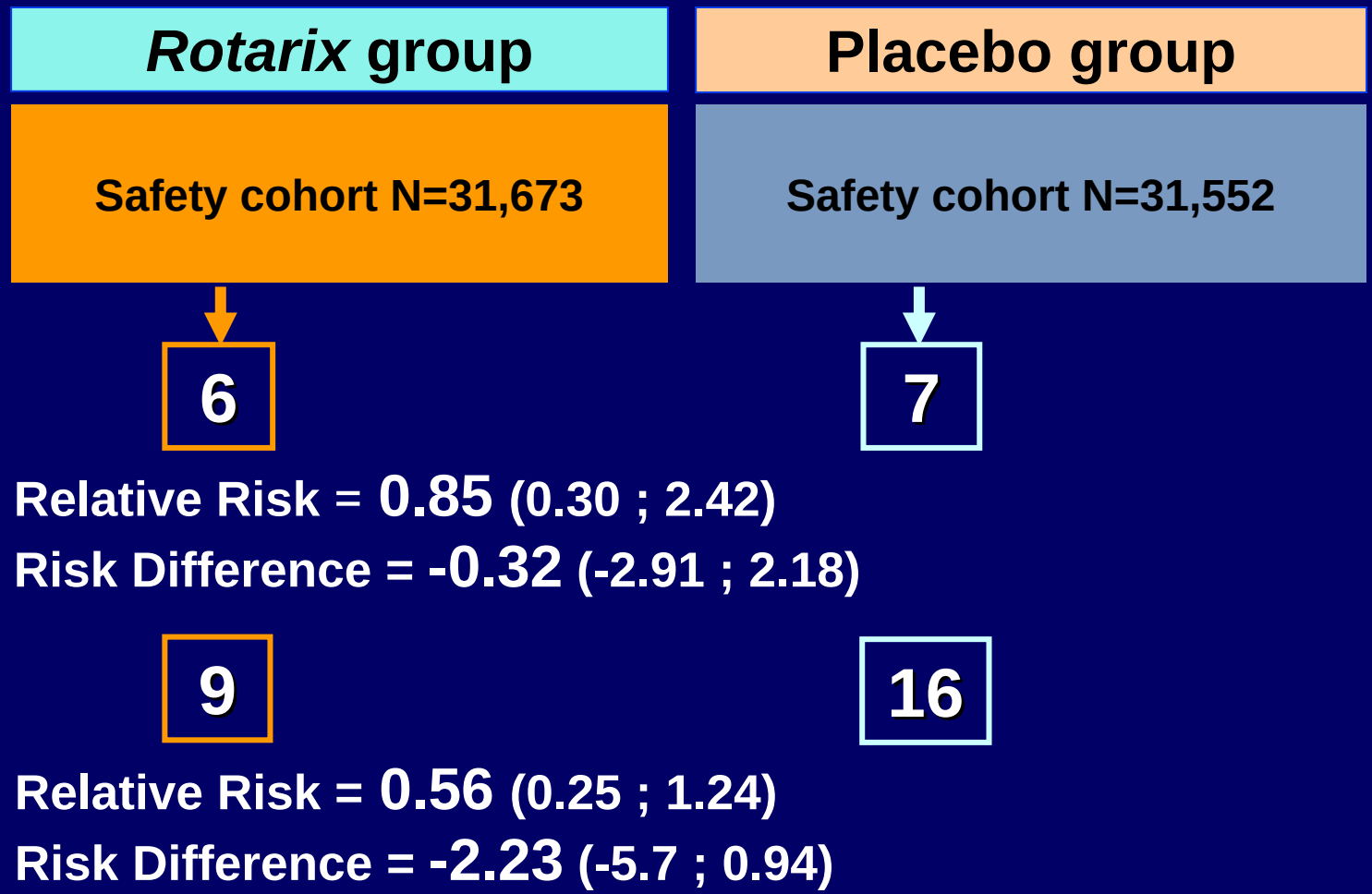
Pre-specified non-inferiority criteria met for <u>all</u> 17 coadministered antigens:

- anti-PRP, anti-HBsAg, anti-poliovirus 1, 2 & 3, anti-D and anti-T: LL of 95% CI for the treatment difference in seroprotection rate ≥ -10%
- anti-PT, anti-FHA and anti-PRN: LL of 95% CI for the GMC ratios ≥0.67
- *S. pneumoniae* serotypes 4, 6B, 9V, 14, 18C, 19F & 23F: LL of 95% CI for the GMC ratios ≥0.5

Overview: Safety Data

- Intussusception: Study 023
- Integrated Summary of Safety: 8 studies

Study 023: No Increased Risk of Intussusception Compared to Placebo



Study 023: No Clustering of IS Cases within 7 or 14 Day Window Post-vaccination

Day Range	Dose 1		Dose 2		Any Dose	
	Rotarix	Placebo	*Rotarix*	Placebo	*Rotarix*	Placebo
	N = 31,673	N = 31,552	N = 29,616	N = 29,465	N = 31,673	N = 31,552
0-7	0	0	2	0	2	0
8-14	0	0	0	2	0	2
15-21	1	1	2	1	3	2
22-30	0	1	1	2	1	3
Total (0-30)	1	2	5	5	6	7

RR= 0.5 (0.07;3.8)
RD= -0.32 (-2.03;1.2)

RR= 0.99 (0.31;3.21)
RD= -0.01 (-2.48;2.45)

RR= 0.85 (0.3;2.42)
RD= -0.32 (-2.91;2.18)

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Integrated Summary of Safety (ISS)

- Based on all RD, placebo-controlled clinical trials in the BLA
- "Core" ISS compares ***Rotarix*** licensure potency to placebo
- 8 clinical trials: US, CA, Latin America, Asia, EU
- Solicited AEs day 0-7 post each vaccination
  - fever, fussiness/irritability, loss of appetite, vomiting, diarrhea, cough/runny nose
- Unsolicited AEs day 0-30 post each vaccination
- SAEs (including IS and fatalities) day 0-30 post each vaccination
- Imbalance defined as exact 95% CI for RR across studies excludes "1"

Core ISS: Most Frequently Reported SAEs Within 31 Days of Any Dose

Adverse Event (MedDRA PT)	*Rotarix* N=36,755	Placebo N=34,454	Relative Risk (95% CI)
	n (%)	n (%)	
At least one SAE	627 (1.71%)	659 (1.91%)	0.90 (0.81 – 1.01)
Bronchiolitis	127 (0.35%)	137 (0.40%)	0.88 (0.68 – 1.13)
Pneumonia	122 (0.33%)	122 (0.35%)	0.99 (0.76 – 1.28)
Gastroenteritis	72 (0.20%)	111 (0.32%)	0.62 (0.45 – 0.84) §

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Relative Risk adjusted for study effect

§ 95% CI for RR excludes 1

Core ISS: SAEs with Imbalance Within 31 Days of Any Dose

Adverse Event (MedDRA PT)	*Rotarix* N=36,755	Placebo N=34,454	Relative Risk (95% CI)
	n (%)	n (%)	
Gastroenteritis	72 (0.20%)	111 (0.32%)	0.62 (0.45 – 0.84) §
Diarrhea	9 (0.02%)	25 (0.07%)	0.35 (0.14 – 0.78) §
Dehydration	9 (0.02%)	21 (0.06%)	0.43 (0.17 – 0.97) §

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Relative Risk adjusted for study effect

§ 95% CI for RR excludes 1

Events of Clinical Interest

Clinical Event	Reason for Interest
Hematochezia	Reports with *RotaShield* *RotaTeq* US Package Insert
Kawasaki disease	*RotaTeq* US Package Insert
Convulsion	*RotaTeq* US Package Insert Imbalance in single study (Rota-023)
Pneumonia deaths	Imbalance in single study (Rota-023)
Pneumonia	Imbalance in single study (Rota-036)
Bronchitis	Imbalance in single study (Rota-006)

Events of Clinical Interest: Core ISS Within 31 Days of Any Dose

Adverse Event (MedDRA PT)	*Rotarix* N=36,755	Placebo N=34,454	Relative Risk (95% CI)
	n (%)	n (%)	
Hematochezia SAE	0	0	-
Kawasaki disease	0	0	-
Convulsion SAE	9 (0.02%)	7 (0.02%)	1.18 (0.39 – 3.76)
Pneumonia deaths	7 (0.02%)	5 (0.01%)	1.39 (0.38 – 5.57)
Pneumonia SAE	122 (0.33%)	122 (0.35%)	0.99 (0.76 – 1.28)
Bronchitis SAE	21 (0.06%)	24 (0.07%)	0.85 (0.45 – 1. 59)

Relative Risk adjusted for study effect

Safety Analysis Study 023

- Multiple comparisons made between groups for exploratory purposes to evaluate potential imbalances within
  - 24 different MedDRA system organ classes (SOCs)
  - 265 different MedDRA preferred terms (PT's)
- Asymptotic p-values used as an aid to highlight potential imbalances worth further clinical assessment
  - no statistical adjustment for multiple testing was made
- Findings have to be interpreted based on overall clinical assessment

Convulsion SAEs

Study Rota-023

- PT "convulsion"
  - From Dose 1 to Visit 3 (30-90 days after Dose 2)
    Rotarix 16 (0.05%), placebo 6 (0.02%); p=0.034*
  - Within 31 days post-vaccination
    Rotarix 7 (0.02%), placebo 5 (0.02%); p=0.568*
- Pooled convulsion-related PTs+
  - From Dose 1 to Visit 3 (30-90 days after Dose 2)
    Rotarix 20 (0.06%), placebo 12 (0.04%); p=0.219*
  - Within 31 days post-vaccination
    Rotarix 7 (0.02%), placebo 9 (0.03%); p=0.798*

* exploratory analysis, not corrected for multiplicity

+ convulsion-related PT = convulsion, epilepsy, grand mal convulsion, status epilepticus, tonic convulsion

Convulsion SAEs – Overall Assessment

- Many subjects in ***Rotarix*** and placebo groups had pre-existing or concurrent medical conditions* that could have accounted for the convulsion
- No temporal association within 31 days after vaccination
- No imbalance with pooled convulsion-related SAEs
- No imbalance in phase III study Rota-036
- No imbalance in core ISS
- Currently available data do not suggest a causal relationship between ***Rotarix*** and convulsion

* neonatal hypoxia, family history of epilepsy, previous convulsion episodes, hypocalcemia and hyponatremia,, chronic malnutrition, seizure after metoclopramide

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Pneumonia Deaths

Study Rota-023:

- Not designed to study the effect of vaccination on fatalities
- Study not controlled for factors associated with higher post-neonatal fatality rate
  - prematurity, age of mother, exposure to smoking, nutritional deficiencies
- From Dose 1 to Visit 3 (30-90 days after Dose 2): pooled pneumonia-related*
  Rotarix 16 (0.05%), placebo 6 (0.02%); p=0.054+

* pneumonia-related PT = pneumonia, bronchopneumonia, pneumonia CMV

+ exploratory analysis, exact p-value, not corrected for multiplicity

Clinical Case Review

Study Rota-023: Pneumonia-related deaths in Rotarix Group

- There were no unique or distinguishing clinical characteristics, or common CXR findings
- Symptom onset of 16 cases
  - 7 between day 0-30; no temporal clustering
  - 9 beyond day 30 (range day 31-199)
- 5 of the 16 had pre-existing conditions, risk factors and/or other alternative diagnoses*

* clinical diagnosis pertussis; CMV in lung tissue on autopsy, mother HIV positive; clinical diagnosis pneumonia, exposed to HIV positive mother with bacterial meningitis; Down syndrome and congenital heart disease; Ependymoma and CSF fistula with nosocomial adenovirus pneumonia

Pneumonia-related* Hospitalizations From Dose 1 to Visit 3 (30-90 days after Dose 2) Study Rota-023

Timing	*Rotarix* (N=29616-31673)		Placebo (N=29465-31552)	
	n	Per 10000	n	Per 10000
Dose 1 to Visit 3	277	87.46	273	86.52
Post-dose 1				
Any time	185	58.41	177	56.10
Within 31 days	99	31.26	94	29.79
Post-dose 2				
Any time	92	31.06	96	32.58
Within 31 days	49	16.55	56	19.01

* all pneumonia-containing PTs within SOC infections and infestations

Ongoing Placebo-Controlled Studies in Africa

Study 022 (S. Africa)

- N=100
- 13 deaths (Rotarix & Placebo)
- 7 pneumonia-related deaths (Rotarix & Placebo)

Study 037 (S. Africa, Malawi)

- N= 4940
- 122 deaths (Rotarix & Placebo)
- 53 pneumonia-related deaths* (Rotarix & Placebo)

- GSK is blinded to treatment allocation
- IDMC stated no safety concern based on review of unblinded data

*data lock point was 31 Dec 2007

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Pneumonia SAE

Study	Sample Size	Event	Time to Onset	*Rotarix* n (%)	Placebo n (%)	RR (95% CI)
036	Rotarix: 2,646 Placebo: 1,348	Pneumonia -related*	within 31 days any dose	3 (0.11%)	1 (0.07%)	1.53 (0.12 – 80)
			within 1 season	14 (0.53%)	4 (0.29%)	1.78 (0.56 – 7.44)
			within 2 seasons	33 (1.25%)	8 (0.59%)	2.1 (0.95 – 5.27)
Core ISS	Rotarix: 36,755 Placebo: 34,554	Pneumonia -related	within 31 days any dose	159 (0.43%)	157 (0.46%)	1.0 (0.79 – 1.25)+
			any	574 (1.56%)	557 (1.62%)	0.99 (0.88 – 1.12)+

* Pneumonia-related = pneumonia, bronchopneumonia, lobar pneumonia, viral pneumonia, bacterial pneumonia

+ Relative Risk adjusted for study effect

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Pneumonia SAE

Rota-028/029/030 Asia	Event	Time to Onset	*Rotarix* N=5359 n (%)	Placebo N=5349 n (%)	p-value
	Pneumonia -related*	within 31 days any dose	2 (0.04)	4 (0.07)	0.413
		within 2 years	63 (1.18)	70 (1.31)	0.534

Rota-024 Latin America	Event	Time to Onset	*Rotarix* N=4376 n (%)	Placebo N=2192 n (%)	p-value
	Pneumonia -related*	within 31 days any dose	33 (0.8)	12 (0.5)	0.338
		within 1 year	138 (3.2)	68 (3.1)	0.910

* Pneumonia-related = all PT under the SOC 'Infections and infestations ' that contains the word 'pneumonia'. In these studies, it contains: Bronchopneumonia, Lobar pneumonia, Pneumonia, Pneumonia adenoviral, Pneumonia bacterial, Pneumonia haemophilus, Pneumonia influenzal, Pneumonia mycoplasmal, Pneumonia respiratory syncytial viral, Pneumonia streptococcal and Pneumonia viral

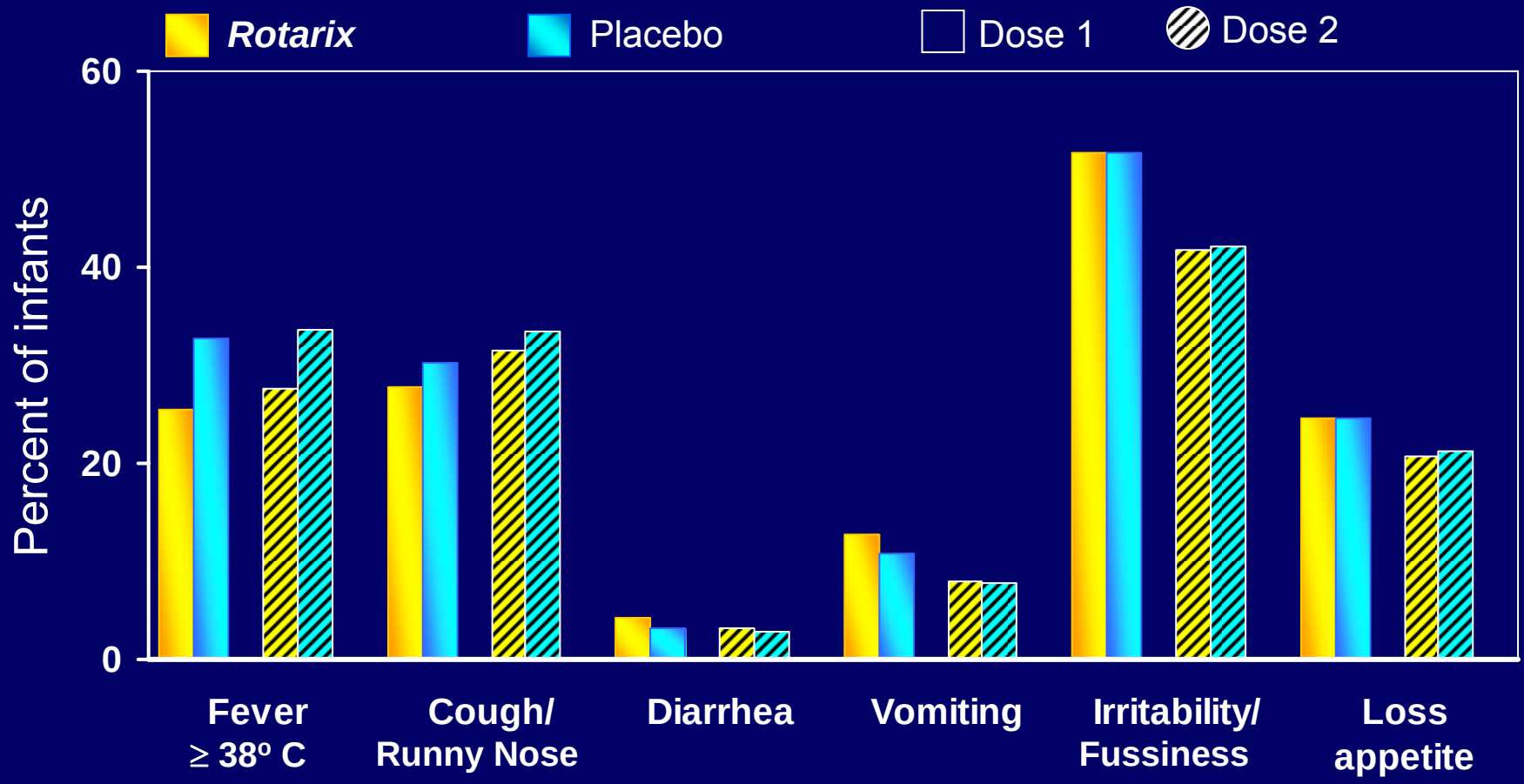
Causality assessment of pneumonia-related deaths and SAEs

- **Consistency**
  - findings isolated to 1 study
- **Strength of association**
  - of marginal statistical significance
  - exploratory analyses, not adjusted for multiplicity
- **Specificity**
  - lower RTIs common in study population
  - multiple etiologies/pathogens
- **Temporal relationship**
  - no temporal clustering within 0-30 days
- **Biological plausibility**
  - no established link between RV and lower RTIs

- Currently available data do not suggest a causal relationship between ***Rotarix*** and pneumonia-related deaths and SAEs
- Further assessment planned in PM setting

Core ISS: Reactogenicity
Solicited Symptoms: Any Intensity

within 8 days post-vaccination



Pharmacovigilance Plan: Overview

- 23.5 million doses distributed (11 January 2008)
- Global Pharmacovigilance Plan for ***Rotarix***

Post-licensure Clinical Studies

Dominican Republic	Transmission of HRV between twins
South Africa	Safety and immunogenicity of HRV in HIV positive infants
Europe	Safety and immunogenicity of HRV in preterm infants

Post-licensure Clinical Studies

Latin America	Safety and Efficacy coadministration with OPV
Asia	Safety and Efficacy
South Africa and Malawi	Safety and Efficacy

Post-licensure Observational Studies: US cohort

- Outcomes of interest: Intussusception, Kawasaki disease, hospitalizations for acute lower respiratory tract infections, convulsions, and deaths from any cause.
- Powered to detect a RR of IS of 2.5 or greater with 80% probability
- Design and study setting under discussion with FDA

Additional Post-licensure Observational Studies

- Intussusception: Mexico
- Intussusception: Surveillance in Germany and the UK
- Vaccine effectiveness: case-control studies in Panama, Belgium and Singapore
- Vaccine strain surveillance: Europe rotavirus surveillance network

Enhanced Pharmacovigilance

- Worldwide network for spontaneous reporting
- Enhanced follow-up of all intussusception cases
- Enhanced reporting to the FDA and CDC

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